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ON THE TEMPERATURE LIMITS OF THE VITALITY OF THE MAMMALIAN HEART. By H. NEWELL MARTIN, M. A., M. D., D. Sc., F. R. S., and E. C. APPLEGARTH, B. A., Fellow of the Johns Hopkins University. With Plates XXIII, XXIV, XXV.

Some years ago one of us[1] published the results of a research showing that between the limits 27° C. and 41° C., the heart of the dog, when isolated from all other organs but the lungs, beats quicker the higher its temperature, so that by heating or cooling the blood supplied to the isolated organ through the superior vena cava, the pulse rate could be controlled.

These earlier experiments made it clear for the range of temperatures above stated, that the tendency to beat quicker at a higher temperature was a fundamental property of the heart, and that the cardiac muscle of the dog agreed in the dependence of its rhythm upon temperature changes with the histologically very different muscle tissue of the frog's heart. A question which then presented itself was, What are the limits of temperature within which the heart of a mammal will beat at all? It also seemed of interest to ascertain whether mammalian cardiac muscle agreed with amphibian in having an optimum temperature at which its rate of beat was quickest, beyond which any increase would slow the rhythm, without necessarily killing the heart. That there was some such optimum for the dog's heart was rendered probable by the fact that in some of the earlier experiments[2] it appeared that heating the organ above 42° C. slowed its beat.

Attempts made three or four years ago to solve these problems were futile, because near the liminal temperatures, high or low, the heart beat with so little force that its death seemed rather due to deficient circulation through the coronary capillaries than to direct influence of heat or cold on the cardiac muscular or nervous tissues. Our problem was, therefore, to keep the cardiac

[1] H. N. M. Phil. Trans. Roy. Soc. 1883, Pt. II, p. 663.
[2] Phil. Trans. 1883, Pt. II, table on p. 681.

presented by the author.

vessels well supplied with blood whether the heart beat feebly or strongly, and at the same time to vary its temperature at will. The first requirement it seemed we might attain by connecting the aortic stump of the isolated heart with a Mariotte flask filled with blood and kept at a constant level above the organ. Under such circumstances a constant pressure would be maintained in the coronary arteries, quite independent of the force of the heart's beat. If this could be done and the heart kept alive, it would be easy to add arrangements for varying the temperature. A preliminary experiment or two having showed that the plan was feasible, we arranged our apparatus essentially as indicated diagrammaticly in Plate XXIII.

The heart was isolated in the manner described in previous numbers of this Journal, and throughout the experiment was contained in a large moist chamber, *A*; part of the roof and of one end of this are indicated at *a* and *a'* in the figure. This chamber has no floor; it sits in a shallow iron trough containing water, which, during an experiment, is heated by Bunsen's burners placed under the trough so as to keep it and the chamber warm, and the air within the chamber saturated with moisture. This air is (so far as necessary occasional opening the doors of the chamber will permit) kept at a temperature ranging between 38° and 40° C. The chamber used was that described in the first number of the fourth volume of these Studies (p. 41), and figured in Plate V accompanying that number. Most accessories had, however, to be changed when the experiments described in this article were undertaken; the Mariotte flasks, for instance, were placed outside the chamber instead of inside it; and a new form of aortic cannula had to be devised.

The animal (cats were used in all cases) was rendered insensible by inhalation of ether or by subcutaneous injection of paraldehyde, and then given curare in some cases, in others not. Paraldehyde in doses of about 5 cc. we found on the whole the most satisfactory. Tracheotomy was next performed (as a preliminary to opening the thorax), and the wind-pipe connected with the apparatus for artificial respiration. The thorax having been opened, and most vessels of the systemic circulation tied essentially as described previously,[1] the glass cannula shown in

[1] Stud. from Biol. Lab., Vol. IV, p. 36.

Plate XXIII was tied into the distal end of the aortic arch. This cannula[1] has three side-pieces; through the one farthest from the heart it is supplied with defibrinated blood from the Mariotte flasks through the rubber tube p; through the next the most of this blood is carried off through the tube q and poured into a funnel; the height of this funnel above the heart of course determines the pressure in the aortic stump. A thermometer was tied into the third branch of the cannula, as shown in the diagram. All branches of the aortic arch except the coronaries were of course closed. The blood supplied to the aortic stump could thus escape only through q into the funnel shown in the plate, or through the circuit q', indicated by dotted lines, and consisting of the coronary vessels. The blood taking the coronary circuit, on reaching the right auricle proceeded to the corresponding ventricle, and from it through the lungs to the left auricle. This blood (that taking circuit q') was therefore the only blood entering the cavities of the heart or passing through the lungs, unless there were some inefficiency of the aortic semilunar valves. That the cavities of the heart were not distended with more blood, we found not to influence the normal character of its beat, which continued in many cases forcibly and rhythmically for three or four hours. The beat of the frog's heart, as well known, is much promoted by moderately high intracardiac pressure; that this is not, at least to so great an extent, the case in mammals seems easily explicable. The frog's heart, having no capillaries, depends for its nourishment or the washing out of its wastes, on the forcing of liquid under pressure into the spongy network of the ventricle, while in the mammal the nourishment of the heart depends on pressure in the aortic arch, from which the coronary system is supplied.

The side tube q is designed to get rid of the difficulty of insufficient aëration of the blood; were it not present, the only flow from the aorta would be through the coronary system, and the flow would be so slow that it would be impossible to renew the blood in the cannula fast enough to keep it from using up its own oxygen and becoming very venous, and unfitted to keep the heart at work. But by a free outflow through q, the

[1] The cannula was modified in the later experiments, as it was found more easy to manipulate when made in two pieces (p. 280).

blood in the cannula is quickly changed, and, moreover, so rapid a bubbling of air through the supplying Mariotte flask secured, that the flask takes the place of a lung and supplies arterial blood. The blood flowing from q into the funnel is collected in a beaker and poured every minute or two into the receiving Mariotte bottle, until the supplying bottle is nearly empty and the other full, then the stop-cocks are reversed and the receiving becomes the supplying bottle, and *vice versa.*

The preceding sketch of the general plan of an experiment will probably be sufficient for most readers. In practice many unforeseen difficulties had to be overcome, which may be of interest to those desiring to further investigate the subject. A primary difficulty, which it took us long to meet successfully, was, that in a progressive heating or cooling experiment, the blood during its circuit changed its temperature so much that we could not, on interchanging the supplying and feeding Mariotte bottles, get a continuous series of observations. This was overcome by an arrangement which poured water of desired temperature into the trough containing the Mariotte bottles; thence it flowed through wide tubes forming water-jackets for the tubes p and q, Pl. XXIII, and then into a water-jacket surrounding the funnel receiving from q, and emptying into the tank containing the beakers, from which the circulating blood was returned to one of the Mariotte bottles. Another difficulty which we soon discovered was that the temperature of the heart was by no means always that of the blood supplied to it; so a thermometer inserted through the *precava*, and with its bulb reaching into the right ventricle, was used to indicate the actual temperature of the heart, instead of the thermometer in the cannula. In the tables which follow, it is the record of the thermometer placed inside the right heart which is given.

The moist chamber (A, Plate XXIV) had on its top the two Mariotte flasks securely fastened in a tin box, B, serving as a water-jacket. One side of B is of glass and turned towards the assistant to enable him to see readily when a flask is nearly empty, so that by reversing the stop-cocks he may convert it from the supplying into the receiving flask. The flasks each hold about 700 cub. cent. From near the bottom of each passes the outflow tube, which is conveyed through the spouts h of the tin box into the warm chamber, and is continued by the rubber tube T (the left one is for the greater part omitted in the plate), to an aperture in the end of the warm chamber through which it passes to one leg of the Y-piece q, Plate XXV. Each upper leg, j, of the Y-piece has a stop-cock on it (bs), so that the supply may be taken from either Mariotte flask at pleasure.

Each Mariotte flask is closed air-tight by a rubber cork pierced by three glass tubes (Plate XXIV); one of these, o, is connected by a Y-piece with the funnel P, from which it gets blood when acting as receiving flask; a second, n, serves to let air out as blood enters the flask; both n and o are of course closed when the flask is acting as supply bottle to the heart. The third tube, m, reaches to near the bottom of the flask, and through it air bubbles in when the flask is acting as supply bottle. From its upper end passes the rubber tube, seen again

at *m* in Fig. 1, Plate XXV, where only the tube of one side is drawn ; of course in actual use there must be a like tube attached to the other Mariotte flask. The long rubber tube *m* passes through the cork of a tightly closed test-tube, *Tb*, containing a little water. Another tube, *at*, passes to near the bottom of the test-tube and is open. When the Mariotte flask is at work all the air entering it must first bubble through the water in the test-tube, which, hanging outside the chest and the water-jacket, is easily observed, and indicates how fast the blood from the flask is flowing, or if the bubbling stop, that something has gone wrong and the supply bottle has ceased to act as a Mariotte flask. It is not necessary to describe in detail the stop-cocks which lie on all the tubes so that they can be in a moment closed or opened when the functions of the two flasks are to be reversed.

All the system of blood-carrying tubes is inclosed in a set of water tubes continuous with the spouts *hh* of *B*, and having warm or cold water from *B* flowing steadily through them during an experiment. Over those ends of each of the spouts which open into the warm chamber is fitted thin rubber tubing 1½ inches in diameter ; these tubes surround the blood-conveying tubes *TT*, and finally end (Fig. 2, Plate XXV) in *J* and *J*, which open into a funnel-shaped tin water-jacket. Inside this jacket the Y-piece *q* (Fig. 1, Plate XXV) is placed, and its upper limbs *jj* pass through *JJ* to join *TT*. On the sides of the tin jacket are openings through which pass the handles (*bdr*, Fig. 2) of the stop-cocks *bs bs* (Fig. 1).

The lower limb *Q*, Fig. 2, Plate XXV, of the tin jacket surrounds *q*, Fig. 1 (which conveys the blood again into the warm chamber) and is continued over *C*. This tube (*C*, Plate XXIV) leads to the aortic cannula *a*, and up to about six inches from that point is jacketed by a wide rubber tube. At this point the jacketing tube is securely closed by a rubber stopper, through which a glass cannula, *a*, continues the blood-carrying system to the aortic stump. The reason for stopping the jacketing for a short distance at this point is to facilitate insertion of the cannula.

So far, then, it will be seen that water supplied to *B*, Plate XXIV, will flow out through the wide tubing surrounding *TT* through the jacket *JJ* (Plate XXV) to the tube around *C*, keeping the blood under essentially the same temperature conditions during its whole journey from the supply bottle to the heart. From near the rubber cork closing the jacket of *C* the water finds its exit through a side branch, a wide rubber tube surrounding *e*, and so to the wide glass funnel *f*, Plate XXIV. This funnel has a short stem into which is accurately fitted the stem of the blood-receiving funnel (*R*) by means of rubber tubing. From *f* the water issues through the outflow piece through the jacketing hose *l* into the tin kettle *y* (Plate XXV) containing the beakers for catching the blood ; and finally into the waste bucket through the tube *Wst*.

The only parts of the blood-conveying system, then, which are not jacketed are the funnel *P*, the tubes *oo* leading from it to the Mariotte bottles, and the cannulas near the heart with a few inches of adjacent tubing. With the exception of the funnel *P*, however, most of these, including the innominate and aortic cannulas, were packed in a layer of cotton wool, thus checking any rapid loss or gain of heat.

All the water-jackets, or rather the whole jacket, for the system is but one, are supplied directly from the water pipe of the room. This pipe by means of a T piece is connected with an air chamber whose capacity is 18 gals., and which is capable of standing a high pressure to the square inch. From the bottom of this chamber a delivery pipe, *W*, Fig. 1, Plate XXV, runs to terminate in the stop-cock *D*, which stands in connection with a two-way stop-cock *C*, by means of which the current of water can be shunted either to the heater, *H*, or in the case of a cooling experiment to a worm (not represented in the figure) placed in a freezing mixture and substituted for the heater. In this way a constant stream of any desired temperature may be obtained.

The heater consists of about 30 feet of small brass pipe wound into a coil and placed over a small Bunsen gas-stove. The stove and coil are entirely surrounded by the screen (*Scr*) provided with its chimney, *H*. Before the water passes to the heater, however, it is made to go through *Ww* to a worm of 25 ft. of ½-inch bore lead pipe put in the hot water of the pan which forms the floor of the moist chamber. After traversing this worm it comes to the heater through *Hw*. In this manner the stream of water can be warmed even before it reaches the heater. The temperature of the water may be regulated by withdrawing the worm totally or in part from the water in the floor of the chamber, by the amount of gas burned, and by the rate of flow of the water. Of course in a cooling experiment this second worm was not used.

After issuing from the heater (or, in the case of cooling experiments, the worm in the freezing mixture) the stream is directed by *Rw* through the registering apparatus (*Rg*) where its temperature is ascertained. This apparatus is simply a T piece, one leg of which carries a thermometer. From this the water passes up *Bw* (Plate XXV) to the jacket *B* (Plate XXIV) and is then distributed over the whole system just described.

Dr (Fig. 1, Plate XXV) is a small sliding door which gives the assistant access to the interior of the case during the experiment. While an experiment is going on, the main doors of the moist chamber are opened as little as possible.

As will be seen, the cannula in Plate XXIV differs in detail from that shown in the diagram Plate XXIII. It is made in two pieces. One, *a*, is inserted in the aortic stump, and receives blood from the Mariotte flask. By its side branch *k* it was in some cases connected with the manometer of a kymograph. The other piece, *i*, is inserted in the innominate artery and contains a thermometer bulb. From it the tube *e* carries off the excess blood to the funnel *R*.

An attempt was made at first to get a graphic record of the pulse, by connecting a manometer with the aortic cannula; but the quantity of blood reaching the left ventricle was so small that the pulse waves due to its beat were indistinct and sometimes imperceptible. We had therefore to resort to counting by direct observation of the heart, which may have led to slight errors when the pulse was very fast and very feeble, but as our object was not to study the absolute pulse rate, small errors in regard to it were of no great importance. Moreover, by always taking two counts immediately following one another the chances of error were greatly lessened. First, one of us held the watch for thirty seconds while the other counted the heart beats. Then the duties were reversed and the other made the count, still being ignorant of the number

arrived at by the previous counter. If the two counts did not agree, but differed only by three or four in a minute, their average was put down in the tables as the correct rate; if the difference was greater (as was sometimes the case when rapid changes of temperature were occurring) a fresh count was made or the observation rejected altogether.

In all cases at least half an hour was allowed to elapse after complete isolation of the heart before the actual experiment commenced. This was in order to eliminate possible disturbing elements, as irritation of the vagi or accelerators, due to the operative procedure, or the first effects on the heart itself of the defibrinated blood. The general results of the experiments can be stated in few words.

First, as to cooling. The isolated heart of the cat may be cooled down to a temperature of 16.5° C. (as indicated by a thermometer introduced into the right heart) and yet not be killed, as it revives if soon warmed again (see Table I, p. 282), but it usually dies at about 17° or 18° C.

As the cooling proceeds, the pulse becomes slower and slower; this has two causes. As pointed out in previous papers, after about the first half-hour the pulse rate of the isolated heart tends to become slower the longer its isolation; so that a dog's heart isolated for one hour and beating, say, 220 times a minute at a temperature of 39° C., will at the end of two hours and at the same temperature beat only 200, or perhaps 190 times a minute. But the slowing in such cases is very gradual, and the heart will beat vigorously for four or five hours if not cooled. When the influence of cold is added, the fall in the pulse rate is far more rapid, and death of the isolated organ, if the cold be continued, occurs much sooner than it otherwise would.

TABLE I.

Cooling experiment with recovery, June 13, 1888.

Adult cat narcotized with paraldehyde during isolation of the heart. Isolation completed at 3.30 P. M.

Time P. M.	Temperature C. in Right Heart.	Pulse per 1′.	Remarks.
h. m.			
4.08	34.0	183	
4.11	33.7	175	
4.14	32.7	158	
4.17	30.9	138	
4.20	29.9	124	
4.23	28.5	111	
4.26	28.5	92	
4.29	26.7	80	
4.32	25.7	74	
4.35	24.7	66	
4.38	24.0	61	
4.41	23.5	54	
4.44	23.0	53	
4.47	22.3	50	
4.50	21.7	40	
4.52	20.5	?	
4.56	19.9	?	
5.00	19.5	12	
5.04	19.2	11	
5.06	18.9	9	
5.12	18.6	9	
5.15	18.0	9	
5.20	16.5	5	Heating now commenced.
5.40	21.0	14	
5.45	24.0	20	
5.50	27.3	78	Contractions becoming very feeble.
5.56	29.7	85	
6.06	31.7	90	

The results obtained on heating the heart to or near to its death point are more complex than those observed on cooling, but also more interesting.

In the first place we found that there was an *optimum* temperature at which the isolated cat's heart, like that of the frog, beat quickest, any rise beyond this slowing the beat. It by no means follows, of course, that this optimum is the temperature at which it would do most work. Averaging the results of thirteen separate experiments, this optimum is 41.3° C., ranging between 43.3 and 40.6.

If one steadily and slowly heats the heart to the highest temperature to which it can be raised without dying, this lethal

temperature lies between 44.5° and 45° C. in the great majority of cases; but sometimes by working with care, one can raise this *maximum* as well as the *optimum* temperature. If as soon as the heat is beginning to slow the pulse, or the heart shows other signs of weakening, the organ be cooled a little for a short time and then heated again, it can often be raised to a higher temperature without being weakened, and the *optimum* temperature also raised. Table II will serve as an example of a simple maximum and optimum experiment, while in Table III is given an example in which the optimum is raised by slightly cooling the heart from near the lethal temperature and then very slowly heating it again. This power of the heart to rapidly accommodate itself to an abnormally high temperature was so surprising to us that we made repeated observations on the matter. Since then we have been informed by friends engaged in the practice of medicine that something similar is frequently seen in persons suffering from remittent fevers. A rise of temperature associated with considerable quickening of the pulse may, later in the disease, be associated with a less marked quickening.

When the temperature of the heart rises to about 40° C., even though the optimum be not yet reached, small increments of temperature often have no effect on the rate of beat of the isolated heart, or the pulse may even become slower: this no doubt is due to that natural gradual slowing of the pulse of the isolated heart, always occurring as time goes on, and referred to above.

Another phenomenon often observed in heating experiments is what we may call a long latent period. An increase of temperature may not show any effect on the pulse rate for a minute or two, then it comes on, though the heart may in the meantime have been slightly cooled. For this reason (even before the optimum is reached) variations in the pulse curve tend to lag a little behind the temperature variations which led to them.

TABLE II.

Simple heating experiment to show optimum and maximum. June 7, 1888. Adult cat. Paraldehyde. Isolation of heart completed at 11.15 A. M.

Time.	Temperature C. in Right Heart.	Pulse per 1′.	Remarks.
h. m.			
11.51	34.1	168	
11.54	34.8	174	
11.57	35.2	186	
12.00	36.5	188	
12.03	36.9	186	
12.06	38.3	189	
12.09	38.8	190	
12.12	40.0	200	
12.15	40.3	201	
12.18	40.5	200	
12.21	40.5	200	
12.24	41.2	203	
12.27	41.2	202	
12.30	41.0	200	
12.33	41.8	206	
12.36	42.5	209	
12.39	43.2	210	Optimum or probably rather above it.
12.42	44.7	160	
12.44	45.7	?	Pauses alternating with periods of very rapid beats impossible to count.
12.47	46.0		Fibrillar contractions.

TABLE III.

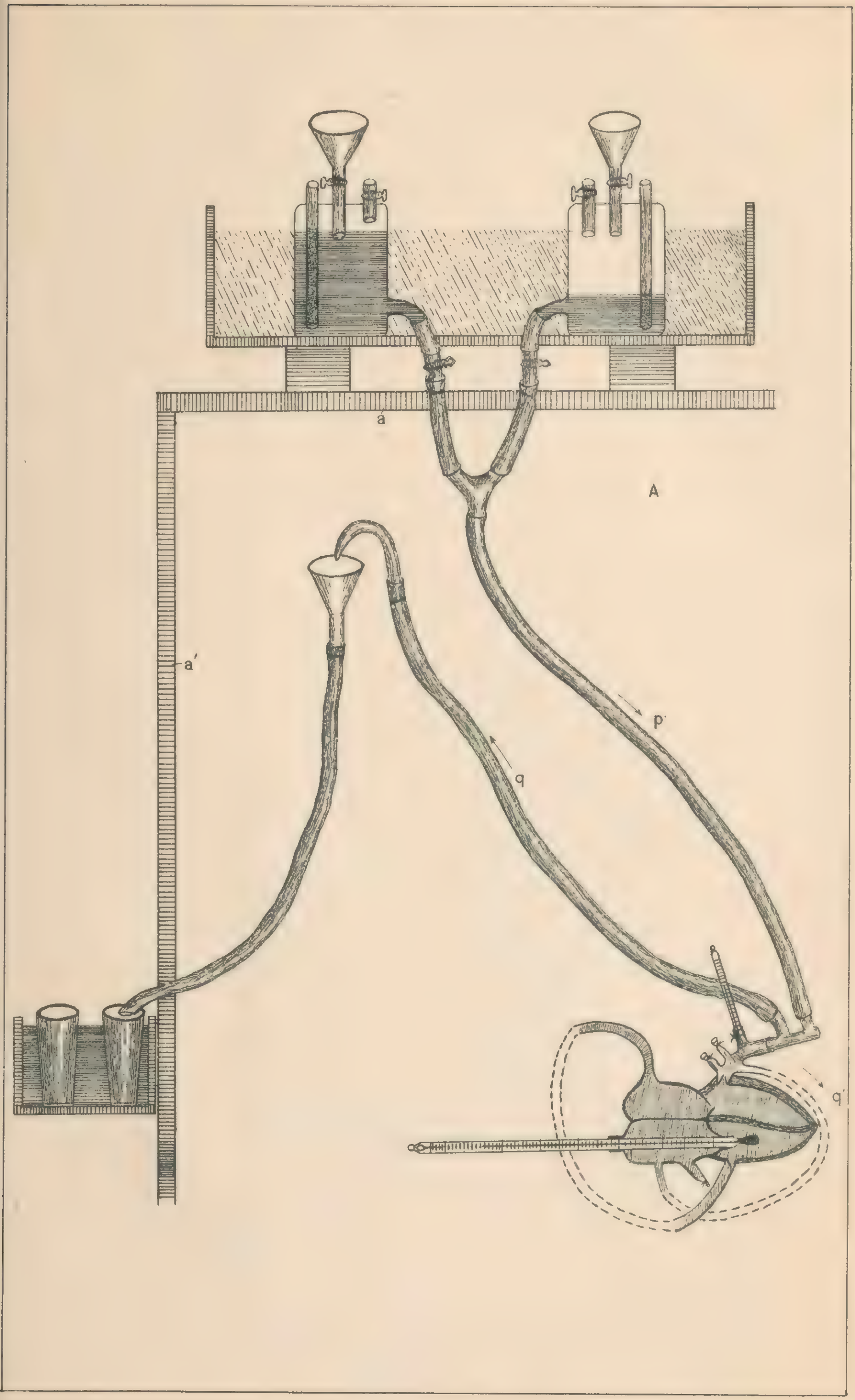
Optimum temperature raised during an experiment. January 31, 1889. Young cat. Ether and curare. Defibrinated blood used to feed the heart, diluted with one-third its volume of normal saline. Isolation completed at 2.55 P. M.

Time.	Temperature C. inside Right Heart.	Pulse per 1′.	Remarks.
h. m.			
3.51	39.3	234	
3.55	39.5	236	
3.58	39.5	220	
4.01	39.8	245	
4.03	40.3	240	
4.06	41.0	292	Temperature now raised with great
4.09	41.0	280	care, as heart is near its critical
4.12	41.0	272	point.
4.15	41.5	304	First optimum.
4.18	41.5	?	Irregular and not countable.

Time.	Temperature C. inside Right Heart.	Pulse per 1′	Remarks.
4.22	41.5	246	Regular. Heart apparently getting used to this temperature.
4.25	41.0	248	
4.28	41.0	204	
4.31	40.5	208	
4.34	41.0	204	
4.37	41.8	224	
4.40	42.0	?	
4.43	42.0	228	
4.46	42.5	234	Second optimum 1° C. above the first.
4.48	42.8	188	
4.51	42.3	198	
4.54	43.0	200 (?)	Somewhat irregular.
4.57	43.5	178	Regular.
5.00	43.0	178	
5.04	42.5	176	
5.07	42.8	176	
5.10	43.0	168	
5.13	44.5		Very irregular.
5.16	44.0	176	Regular.
5.19	48.0	172	Very irregular but not feeble beats; the irregularity probably due to the rapid change of temperature.
5.21			Only right auricle beating.

It is, of course, not possible to say at what temperature the heart of Table III would have died had the heat been slowly pushed on at $4^h\ 18^m$, instead of stopping and cooling from $4^h\ 25^m$ to $4^h\ 34^m$, thus giving the organ time to accommodate itself to the high temperature. But from many other observations in which the heating was slowly pushed on, we feel sure that all pulsation would have ceased at a temperature several degrees below 48° C.

It will be observed that though the temperature of the second optimum is higher than that of the first, the pulse is slower, this being no doubt due to the increasing malnutrition of the heart as time goes on.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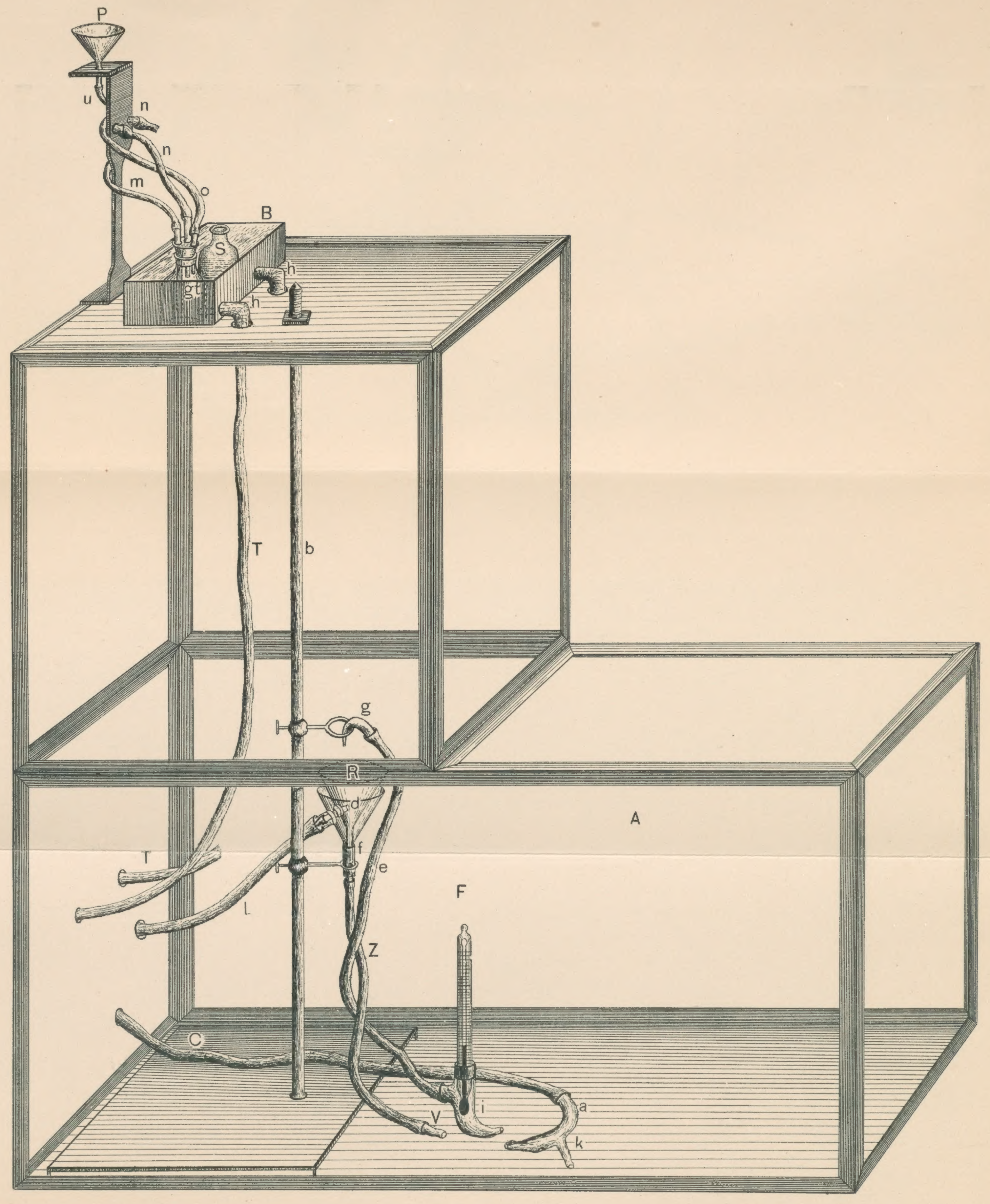
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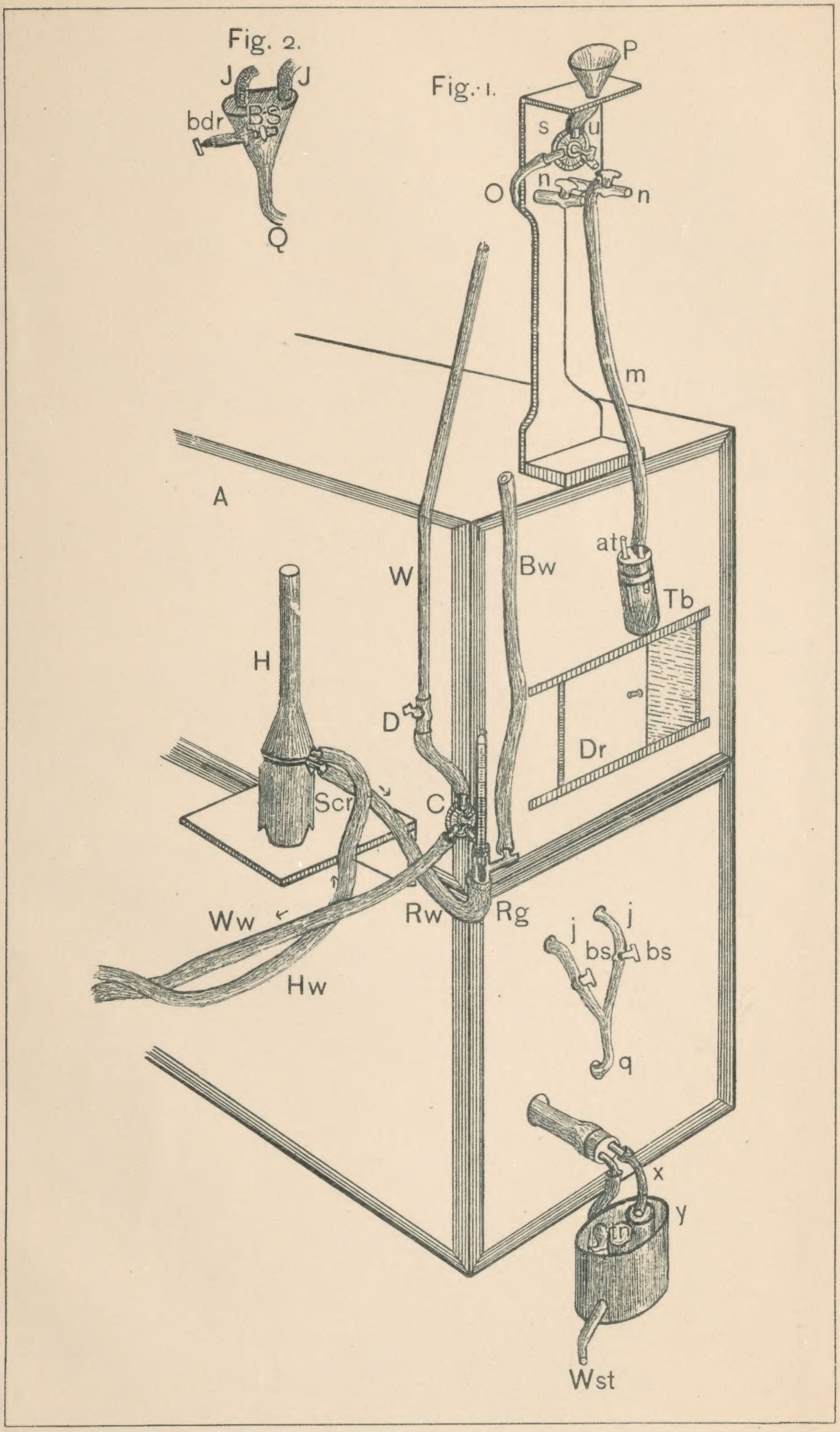
Fig. 2.
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